

Autoimmune lymphoproliferative syndrome

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INTRODUCTION

Autoimmune lymphoproliferative syndrome (ALPS) is a rare disease occurring especially in early childhood, which is defined by the triad of chronic non-malignant enlargement of lymph nodes and spleen; increased number of double negative T cells (DNTs) that express the α/β T cell receptors but lack both the CD4 and CD8 surface molecules (α/β^+ DNTs); and impaired lymphocyte apoptosis in vitro ^[1-5]. Individuals with ALPS frequently suffer autoimmune complications, primarily hemolytic anemia and thrombocytopenia. They also have an elevated incidence of Hodgkin's and non-Hodgkin's lymphoma ^[4-7]. The etiology of ALPS has been attributed to dysregulation of lymphocyte homeostasis due to a primary defect in Fas-induced apoptosis ^[1,2,8].

Historical background

The disease is also described as Canale-Smith syndrome, since Canale and Smith reported five cases with lymphadenopathy, splenomegaly, and autoimmune cytopenias in 1967 ^[6]. In 1992, investigation of two similar patients with progressive lymphoproliferative disease and autoimmunity by Sneller et al. ^[7] revealed an increase in a normally rare population of α/β^+ DNTs, and they proposed that these patients may exhibit the human equivalent of a murine disease caused by the *lpr* (lymphoproliferation phenotype) and *gld* (generalized lymphoproliferative disease phenotype) mutations. In the same year, it was demonstrated that *lpr* mice lacked cell surface expression of Fas, a receptor which causes apoptosis of activated lymphocytes ^[8]. In 1995, Rieux-Laucat et al. ^[1] and Fisher et al. ^[2] documented that this novel disorder was associated with inherited mutations in the Fas gene. Recently, several patients with a clinical syndrome of ALPS have been found to have a normal Fas gene, and further investigations revealed new mutations in other intermediates in the Fas signalling pathway, such as Fas ligand (FasL) gene mutation and caspase 8 or 10 gene mutations ^[9,10].

Lymphocyte apoptosis

ALPS is the first human disease in which the etiology has been attributed to a primary defect in apoptosis. Apoptosis is a genetically determined program of cell death responsible for the control of cell number and elimination of senescent or unwanted cells without causing inflammation ^[11]. In mature T lymphocytes, apoptosis occurs by two major pathways: an extrinsic (active) mechanism mediated by membrane receptors of the tumor necrosis factor receptor superfamily (TNFRSF) and their ligands belonging to the tumor necrosis factor superfamily (TNFSF), and an intrinsic (passive) cell death following cytokine withdrawal after antigenic clearance, mediated by Bcl-2 family proteins ^[12]. Furthermore, perforin, which forms channel-like structures in the target cell membrane, and granzymes, which

Table 1. Criteria for the diagnosis of autoimmune lymphoproliferative syndrome

Required features	
Chronic non-malignant lymphadenopathy, splenomegaly, or both	
Increase ($\geq 1\%$) in circulating T cells that are CD4 ⁺ CD8 ⁻ and express the α/β^+ T cell receptor (α/β^+ DNTs) and/or presence of DNTs in lymphoid tissue	
Demonstration of defective antigen-induced lymphocyte apoptosis on in vitro culture	
Supporting features	
Family history of autoimmune lymphoproliferative syndrome	
Typical findings on histopathologic analysis of lymph node or splenic tissue	
Autoimmune disease	
Mutations of genes encoding Fas or related apoptosis signalling proteins	

penetrate into the target cell through the perforin channels and directly activate the caspase cascade, induce apoptosis in cytotoxic cells^[13].

The TNFRSF comprises more than 20 members, such as Fas, DR3, DR4, DR5, DR6, TNFR1, and TNFR2, and these receptors are the best known death receptors^[13]. Fas (also termed TNFRSF6, CD95, Apo-1) is the best studied member of the TNFRSF, containing one death domain and three cysteine-rich domains. Fas forms homotrimers on the cell membrane upon ligation by its ligand (FasL). FasL is a trimeric type-II surface protein belonging to the TNFSF and is released in soluble form upon metalloproteinase-mediated cleavage. Fas triggering induces formation of a trimolecular complex named death-inducing signalling complex in the cell and this complex triggers the autocatalytic cleavage of procaspase 8 or 10 and release of active caspase 8 or 10. Active caspase 8 or 10 cleaves several cytosolic proteins including procaspase 3 and 7 and drives the cell death program^[13-18]. Activation of caspase 8 may also trigger the intrinsic pathway by cleaving the cytosolic Bid, a proapoptotic molecule belonging to the Bcl-2 family and releasing a fragment (tBid) that translocates to mitochondria and activates the intrinsic pathway. Also, Fas triggering seems to activate an acidic sphingomyelinase and produce ceramide, which alters mitochondria. Therefore, cleavage of Bid and production of ceramide bridge the extrinsic and intrinsic pathways of cell death and serve as a positive loop by amplifying activation of the effector caspases^[13,19,20].

Fas is expressed on the surface of activated T and B lymphocytes and Fas/FasL induced apoptosis is important for eliminating autoreactive immature T cells during ontogenesis and for maintaining peripheral lymphocyte homeosta-

sis^[15]. Resting T lymphocytes express low levels of Fas and high levels of Bcl-2 and c-FLIP, and are a negative regulator of Fas signalling. After an antigenic stimulus, expression of Fas at high levels, induction of the FasL gene, and concomitant downregulation of Bcl-2 and c-FLIP levels occur. In early phases of lymphocyte activation, apoptosis does not occur until ligation of Fas by FasL presents on the cell surface and Bcl-2 and c-FLIP levels are downregulated. High interleukin (IL)-2 levels control the down-modulation of c-FLIP expression. In this way, activated lymphocytes are killed, the immune response can be controlled, and the expanded lymphocytes are partly eliminated. Alternatively, if the activated T lymphocytes are not re-stimulated, IL-2 levels decrease and the cells die by intrinsic apoptotic mechanism^[12,13]. Although Fas appears to be the principal death receptor involved in T cell apoptosis, other death receptors such as TNFR1, DR3, TNF-related apoptosis-inducing ligand (Trail)-R1, and Trail-R2 contribute proapoptotic signals and play a role in lymphocyte apoptosis^[13].

Diagnostic criteria

Diagnostic criteria used by the National Institutes of Health (NIH) ALPS Group are presented in Table 1^[4,21]. Diagnostic work-up includes evaluation of proband and family members through clinical and laboratory testing for required features of ALPS, which consists of immunophenotyping of peripheral blood for enumeration of DNTs and in vitro apoptosis assay as well as detailed molecular genetic analysis for mutations detected previously in ALPS patients. The identification of an increase in DNTs on fluorescent activated cell sorting is a useful screening tool if combined with appropriate clinical features.

Table 2. Clinical features in 79 patients with autoimmune lymphoproliferative syndrome [modified from Sneller *et al.* 2003^[10]]

Sex	
Female	43
Male	36
Median age at presentation (range)	2 y (birth-15 y)
Manifestation	
Lymphoproliferative disease	79 (100)
Splenomegaly	75 (95)
Lymphadenopathy	76 (96)
Hepatomegaly	57 (72)
Lymphoma	7 (9)
Autoantibodies	64 (81)
Anticardiolipin antibody	51 (65)
Positive direct Coombs test	40 (51)
Antinuclear antibody	20 (25)
Rheumatoid factor	11 (14)
Anti-Factor VIII	1 (1)
Autoimmune disease	37 (47)
Hemolytic anemia	23 (29)
Idiopathic thrombocytopenic purpura	18 (23)
Neutropenia	15 (19)
Glomerulonephritis	2 (3)
Optic neuritis or uveitis	2 (3)
Guillain-Barré Ssyndrome	1 (1)
Primary biliary cirrhosis	1 (1)
Coagulopathy/Factor VIII inhibitor	1 (1)

Data compiled from probands and relatives with autoimmune lymphoproliferative syndrome (47 discrete families).

Clinical and laboratory features

The median age at presentation in the NIH cohort is 24 months, ranging from birth to 15 years, with a mild male dominance^[10]. A more frequent diagnosis of adult patients with autoimmune complications has been observed recently^[22]. Prominent non-malignant lymphadenopathy in ALPS arises typically in early childhood and is often accompanied by splenomegaly (in some cases with hepatomegaly) and autoimmune cytopenias of one or more lineages^[21,23-26]. Several non-hematological autoimmune diseases have also been reported in association with ALPS, including glomerulonephritis, uveitis, Guillain-Barré syndrome, autoimmune liver disease, urticaria, panniculitis, and arthritis^[10,21]. The range of clinical features of ALPS is shown in Table 2^[10]. The clinical features of ALPS appear to differ

based on the several different molecular abnormalities and other genetic events which have not been determined yet.

Lymphoproliferation is often the most salient manifestation in ALPS patients. The degree of lymphadenopathy is variable. It ranges from the upper limits of normal for age, to massive anatomically distorting swellings. Lymphadenopathy most often involves the anterior and posterior cervical axillary chains. On examination, the lymph nodes are usually firm, nontender, mobile, and nonsuppurative. Enlargement of abdominal and thoracic lymph nodes is also often found by ultrasound and computerized tomography^[21,27]. The lymphoid hyperplasia is chronic and consistent and reductions may be seen in association with infections. It is not usually associ-

Table 3. Genotype-based autoimmune lymphoproliferative syndrome classification adopted by the National Institutes of Health Autoimmune Lymphoproliferative Syndrome Group

Classification	Abnormality
Type Ia	Mutation on TNFRSF6 (Fas) gene
Type Ib	Mutation on TNFSF6 (FasL) gene
Type II	Mutation on caspase 8 or 10 genes
Type III	No known mutation

ated with systemic symptoms, such as fever or night sweats. Lymphadenopathy is usually more pronounced in infancy, often regresses during adolescence and in some patients spontaneous resolution has been seen, even in the absence of treatment^[21,23]. It has been hypothesized that either the predominant influx of naïve T and B cells in early childhood favors lymphocyte accumulation in comparison to adults and/or that alternative apoptotic pathways are used by human lymphocytes later in life^[10]. In the rare cases of homozygous Fas mutations, prenatal severe lymphoproliferation was observed, indicating that the process started in the prenatal period^[28,29].

Isolated splenomegaly is uncommon, but may dominate the lymphoproliferation in ALPS at some time during the course of the disease. Also, splenomegaly may develop without lymphadenopathy. Splenomegaly may cause blood cytopenias caused by hypersplenism. Hepatomegaly is not usually associated with liver function abnormalities unless associated with autoimmune hepatitis^[30,31]. In severe cases, pulmonary infiltrate can be related to lymphoproliferation^[28].

Autoimmune manifestations are the second most frequent event in ALPS patients. The most common autoimmune manifestations involve hematological lineages leading to anemia, thrombocytopenia, and neutropenia, and are associated with relevant autoantibodies^[5, 28,32]. A delay may occur between the lymphoproliferative phase of ALPS and the development of autoimmunity. Autoimmunity is more likely to occur as patients get older and it is often characterized by exacerbations and remissions^[21]. Autoimmune hemolytic anemia (AIHA) is associated with IgG autoantibodies to red blood cells and is frequently severe. Likewise, idiopathic thrombocytopenic purpura (ITP) is often severe, with platelet counts frequently falling below $20 \times 10^9/L$. AIHA

and ITP may occur concomitantly or as separate events, as in Evans syndrome. Immune neutropenia is another frequent finding in ALPS^[10, 21]. Neutropenia also results from hypersplenism, but it is rarely severe enough to cause infectious complications^[33]. Anticardiolipin antibodies are also frequently seen, but thromboembolic events are rare in patients with ALPS, and have been described in only one ALPS patient^[10]. Infrequent autoimmune manifestations include hepatitis, uveitis, Guillain-Barré syndrome, anti-factor VIII antibodies, and glomerulonephritis^[5,10,33,34]. In ALPS, the potential exists for multiple autoimmune diseases involving different organ systems to occur in a single patient^[10].

Demonstration of an *in vitro* defect in Fas-mediated lymphocyte apoptosis is an absolute requirement for the diagnosis of ALPS. The assay used requires mitogen activation of peripheral blood mononuclear cells followed by additional culturing in IL-2 for a week to sensitize the cells to Fas killing. At the end of this culture period, the Fas receptor is cross-linked using an anti-Fas monoclonal antibody for 12 hours and the degree of cell death measured^[5]. The majority of normal cells are killed, whereas the minority of cells from patients with ALPS undergo apoptosis^[10].

The immunophenotypic finding required for the diagnosis of ALPS is increased levels of circulating α/β^+ DNT cells^[35,36]. The DNTs express the B220, CD57 and human leukocyte antigen (HLA)-DR markers^[35]. Those cells are hypoproliferative and have a decreased capacity to secrete cytokines in response to *in vitro* stimulation, but there is evidence that they secrete large amounts of IL-10 *in vivo*^[5,37]. Other abnormalities present in T cells include high expression of HLA-DR, CD57, CD45RA, CD27, CD28, and perforin; low expression of CD25; and no expression of CD45 RO and CD56^[35]. CD45RA, CD57, perforin, and

HLA-DR expression suggests a cytotoxic T cell phenotype that has lost CD8 expression. CD57 has been associated with aging and senescent T cells, and the high levels of CD57 expression (>75%) on DNTs support the theory that these cells are post-terminally differentiated cytotoxic T cells^[38]. The low expression of CD25 appears to be caused by a selective reduction of the CD4⁺CD25⁺ population and correlates with the severity of clinical features in ALPS^[36]. In addition, increased numbers of CD8 cells and B cells expressing CD5, like in other autoimmune diseases, are common findings^[36].

Several cytokine abnormalities have been found in patients with ALPS, the most striking of which is a significantly elevated IL-10. Overexpression of IL-10 may be involved in the proliferation of autoimmune B cells and may cause the persistence and activation of malignant and autoimmune cell clones. Other cytokine abnormalities support a Th-2 cell skewing and include increased IL-4, IL-5 and decreased INF- γ , IL-12 production by mononuclear cells in vitro^[21,34,39].

The increased levels of IgG, IgA, and IgM (often normal or decreased), increased level of soluble FasL, decreased level of soluble Fas, and decreased in vitro lymphocyte function are other reported abnormalities in patients with ALPS^[5,9,21,23].

Certain histopathologic features help to distinguish ALPS from other lymphoproliferative diseases. Lymph node biopsies of patients with ALPS reveal retention of lymph node architectural features with marked paracortical T-zone expansion ranging from small cells to lymphoblasts. The majority of these cells are DNTs with an identical phenotype to the circulating α/β^+ DNTs, showing very little apoptosis. Marked follicular hyperplasia and plasmacytosis are other changes in the reactive germinal centers. A histiocyte infiltration characteristic of Rosai-Dorfman disease has also been found in some patients with ALPS^[40-42]. The spleens are enlarged, with both the white and red pulps expanded and infiltrated by DNTs, which are phenotypically identical to those seen in the lymph node paracortical regions^[40]. In some patients, liver biopsies also reveal infiltration by DNTs, extramedullary hematopoiesis, and signs of hepatitis. Bone marrow smears have shown increased erythroid hyperplasia during episodes of active hemolysis, an increase in megakaryocytes in response to

thrombocytopenia, and the presence of varying numbers of DNTs, plasma cells, and eosinophils^[40,41]. The liver and bone marrow biopsies are not diagnostic in ALPS.

Patients with ALPS have a significantly higher risk of developing lymphoma than the general population (14 times greater for non-Hodgkin's lymphoma and 51 times greater for Hodgkin's lymphoma)^[43,44]. The risk appears to be life-long and a patient with ALPS may develop two different lymphomas. The response to therapy in ALPS-associated lymphoma is no different than in non-ALPS patients^[43]. The patients with germline mutation of the intracellular domain of Fas have the highest risk of developing lymphoma^[43,45]. Among the cohort of 200 patients seen at NIH, 11 have developed lymphomas, with a median age of 17 years (range 2-50 years)^[46]. Leukemia, thyroid cancer, hepatocellular carcinoma, breast cancer, colon cancer, lung cancer, basal cell carcinoma of the skin and squamous cell carcinoma of the tongue, and glioma-like tumor are other malignancies which have developed in patients with ALPS^[21,24,47-49].

Genetics and genotype/phenotype relationships

The majority of ALPS cases are associated with heterozygous mutations in the TNFRSF6 gene encoding Fas (located on chromosome 10q24.1)^[1,23,24]. Over 70 different Fas gene mutations have now been described in ALPS patients, two-thirds of them in the intracellular domain (ICD) and one-third in the extracellular domains (ECD). The vast majority of these are insertions, substitutions or deletions of one or two base pairs in exons or splice sites of the gene^[33,42]. There is a complex relationship between genotype, phenotype, and disease penetrance. Detailed analysis of extended pedigrees of patients with ALPS has revealed an autosomal dominant inheritance pattern with incomplete penetrance in the majority of cases and recessive inheritance pattern in occasional cases^[23,24,28,30,50]. In large kindreds studied by NIH and French groups, family members with the same mutation showed very different clinical phenotypes^[2,23,24]. This data provides clear evidence that other factors, genetic and/or environmental, influence the clinical phenotype, and a "second signal" is required for the full development of clinical ALPS^[24,33,42]. Recently, it has been demonstrated that polymorphisms in the osteopontin gene might increase susceptibility for the development of an ALPS-like disease

^[51]. Also, in a case with ALPS and lymphoma, inherited perforin mutation was detected ^[52]. After this index case was reported, the same authors studied the variations of the perforin gene in patients with defective Fas function and their data has suggested that perforin variations are a susceptibility factor for ALPS development and may influence disease expression ^[53].

In ALPS, clinical penetration is highest with ICD mutations, with missense mutations causing symptoms in 90%, and truncation mutations causing symptoms in 70%; ECD mutations have demonstrated a clinical penetration of 30% ^[23,30,42,54]. Although the clinical penetration is varied, there is 100% penetration in functional assays with all carriers of Fas mutations having defective Fas-induced T cell apoptosis. The degree of apoptosis, hypergammaglobulinemia, and the number of α/β^+ DNT cells in peripheral blood are again varied, even for the same mutation in different individuals ^[33,42]. Four patients have been described with homozygous Fas mutations who demonstrated a more severe phenotype, with antenatal onset of lymphoproliferation, hydrops fetalis, lymphocytic pulmonary infiltrates, and severe blood cytopenias from birth ^[10,28,29,55].

In a minority of ALPS cases, the TNFRSF6 gene is normal, and among these, one patient who had a clinical presentation resembling systemic lupus erythematosus was found with mutation in the FasL ^[56]. In addition, two patients with ALPS had mutations in the gene encoding caspase 10 ^[57]. These two patients developed lymphoproliferation and autoimmune cytopenias from the first year of life. In addition to having Fas-mediated apoptosis, these patients demonstrated inhibition of death signalling via TNFR1, DR3, Trail-R1 and Trail-R2 ^[42]. In a recent study, genetic variations in caspase 10 in ALPS patients were investigated and it was demonstrated that genetic alterations in caspase 10 may produce contrasting phenotypic effects, which may be causative or protective in ALPS ^[58]. Recently, inherited genetic deficiency of caspase 8 has been reported in a single kindred, and unlike other people with ALPS, two siblings with caspase 8 mutation suffered from recurrent Herpes simplex virus and bacterial sinopulmonary infections, had poor responses to immunization, and had defective activation of T, B, and natural killer cells ^[59]. These findings led the authors in the NIH Group to propose a classification scheme based on the several different molecular abnormalities ^[10]. Patients with mutations in the Fas (TNFRSF6)

gene are classified as type Ia, FasL (TNFF6) as type Ib, caspase 8 or 10 as type II and patients without known mutation are classified as type III (Table 3) ^[10]. Since most ALPS type Ia patients display heterozygous mutations of Fas, some authors have suggested classifying patients with homozygous null mutations (complete Fas deficiency) as ALPS type O ^[34,50]. Several unrelated patients with an ALPS-like clinical pattern but lacking expansion of α/β^+ DNTs and Fas/FasL mutations have been identified, and this disease has been named Dianszani's autoimmune lymphoproliferative disease ^[60].

Recently, it has been reported that a number of patients with Evans syndrome may have ALPS, since in one study, 7/12 (58%) patients with Evans syndrome had elevated DNTs, suggestive of ALPS, with genetic confirmation in 6/7 ^[61]. Also, determination of defective FasL-mediated apoptosis related to a mutation of the human FasL gene in an adult patient with systemic lupus erythematosus and lymphoproliferative disease ^[56] demonstrates that differential diagnosis of ALPS and other autoimmune diseases may be difficult and that genetic studies may be required for final diagnosis.

Differential diagnosis

Presentation of children with generalized lymphadenopathy, splenomegaly, and autoimmune multilineage cytopenias represents a diagnostic challenge because their clinical and laboratory features overlap with and may manifest as those of other childhood diseases, including systemic infections, collagen vascular diseases, lymphoma, Evans syndrome, and Rosai-Dorfman disease. Other immunological disorders that must be differentiated from ALPS include common variable immunodeficiency, Wiskott-Aldrich syndrome, IL-2 receptor α -chain deficiency, angioimmunoblastic lymphadenopathy with dysproteinemia, and the X-linked immunodysregulation-polyendocrinopathy-enteropathy syndrome ^[46,62].

Treatment

Treatment modalities for ALPS are directed at the chronic and persistent lymphoproliferation, autoimmunity, and malignancies. Lymphoproliferation does respond to corticosteroids and other immunosuppressants like azathioprine, cyclosporine or mycophenolate mofetil, but symptoms recur upon dose reduction, and long-term side effects outweigh benefits unless

lymphoproliferation is causing critical obstructive disease^[33,42,46]. Though the use of Fansidar was reported in a small series of patients with ALPS and ALPS-like conditions to be associated with reductions in lymphoproliferation^[63,64], the NIH ALPS Group has failed to show regression of lymphadenopathy or splenomegaly with Fansidar therapy^[46]. One of our ALPS patients reported previously in the literature^[25] also failed to show a positive clinical response to Fansidar therapy. In patients with splenomegaly, the preference is to avoid splenectomy. To reduce risk of splenic rupture, aggressive contact sports are strongly discouraged and a fiberglass abdominal guard is recommended^[10,33,42]. Approximately half of the 200 ALPS patients being followed in the NIH clinic have undergone splenectomy in order to manage recurring and chronic cytopenias, nearly 75% of whom achieved long-term remission. Five asplenic ALPS patients had fatal opportunistic infections and many others presented with pneumococcal sepsis following splenectomy^[46]. Thus, splenectomy should be avoided unless it is the only remaining measure to control chronic, refractory, life-threatening cytopenias. Based upon the NIH ALPS Group's experience, all asplenic ALPS patients must be maintained on long-term antibiotic prophylaxis against pneumococcal sepsis using penicillin V or fluoroquinolones. Their recommendations also include periodic surveillance of antipneumococcal titers and reimmunization against pneumococci using a combination of both 7-valent conjugate (Prevenar) and 23-valent polysaccharide (Pneumovax) vaccines^[46].

The treatment of all autoimmune manifestations is the same as in patients without ALPS. Autoimmune cytopathies respond well to corticosteroids. High-dose pulse therapy with IV methylprednisolone (5-30 mg/kg/d) followed by low-dose oral prednisone (1-2 mg/kg) maintenance that can often be successfully tapered over several months is the most recommended treatment regimen^[21,33,42,46]. In some cases, it is possible to taper and discontinue glucocorticoid therapy over a period of 10 to 14 days. In others, tapering leads to prompt relapses and the need for extended steroid therapy at the lowest possible daily or alternate day dosing. For all patients on prolonged (> 3 months) glucocorticoid therapy, the authors provide calcium and vitamin D supplementation and in adults, bisphosphonate drugs, for prevention of therapy-induced osteoporosis^[10]. Packed red blood cell transfusion support may be needed in cases with severe red

cell destruction^[42]. When blood transfusion is required, it has been recommended that blood should be ABO- and D-compatible, negative to any antigen to which the patient has autoantibodies and matched for C, E, and K antigens^[32]. Immune thrombocytopenia is less sensitive to intravenous immunoglobulin (IVIg) therapy than conventional ITP (10). IVIg (1-2 g/kg) given concomitantly with pulse dose methylprednisolone may benefit some patients with severe AIHA and ITP^[46]. Some ALPS patients with chronic neutropenia and recurrent infections benefit from thrice weekly, low dose (1-2 µg/kg/d) recombinant granulocyte colony stimulating factor^[42,46].

Several of the patients with ALPS and immune cytopenias have required the addition of cytotoxic agents such as azathioprine, cyclophosphamide or cyclosporine^[21]. A young man who showed minimal response to steroids and cyclosporine was successfully treated with recombinant α -interferon therapy^[65]. In addition to a case report of successful use of Rituximab and Vincristine in a single patient with ALPS^[66], the NIH ALPS Group gave Rituximab (375 mg/m²/wk x 4) for refractory, chronic cytopenias to five ALPS patients, and two of them showed durable responses^[46]. Recently, the successful use of mycophenolate mofetil (MMF; 600 mg/m²/dose twice daily) for chronic, refractory immune cytopenias in 13 children with ALPS has been described^[67]. Twelve responded to MMF for a median follow-up of 49 weeks (range 38-240 weeks). In some patients, MMF allowed splenectomy to be avoided or at least postponed in very young children until an age when they could better tolerate asplenia. Stem cell transplantation was successful in two children (one of whom was homozygous) with very severe and refractory cytopenias^[68,69].

Prognosis

Despite the often impressive lymphadenopathy and splenomegaly, the prognosis with regard to lymphoproliferation is typically good. Most patients demonstrate regression of lymphoproliferation even in the absence of treatment. The chronic cytopenias seen in many ALPS patients may improve with age and continue to respond to conventional immunosuppressive treatment. Whether autoimmune manifestations can undergo permanent remission remains to be seen^[10,21,23,46].

The major determinants of morbidity and mortality in ALPS are the severity of the autoimmune disease, hypersplenism, asplenia-related sepsis, and development of lymphoma^[46]. Careful long-term surveillance in patients with mutations abrogating function of the ICD of the Fas protein is especially required, through monitoring of their lymphadenopathy, since these patients are at high risk of developing lymphomas. Noninvasive tests to differentiate benign from malignant lymphadenopathies are needed to help physicians discern whether a biopsy is warranted and of which node. Positron emission tomography using fluorodeoxyglucose (FDG) does not imply presence of lymphoma, since FDG avidity of benign lymph nodes can be high in ALPS, but it can help in deciding which of many enlarged nodes in ALPS patients to biopsy when lymphoma is suspected^[70].

References

- Rieux-Laucat F, Le Deist F, Hivroz C, Roberts IA, Debatin KM, Fischer A, de Villartay JP. Mutations in Fas associated with human lymphoproliferative syndrome and autoimmunity. *Science* 1995;268:1347-9.
- Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM. Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. *Cell* 1995;81:935-46.
- Drappa J, Vaishnav AK, Sullivan KE, Chu JL, Elkon KB. Fas gene mutations in the Canale-Smith syndrome, an inherited lymphoproliferative disorder associated with autoimmunity. *N Engl J Med* 1996;335:1643-9.
- Straus SE, Sneller M, Lenardo MJ, Puck JM, Strober W. An inherited disorder of lymphocyte apoptosis: the autoimmune lymphoproliferative syndrome. *Ann Intern Med* 1999;130:591-601.
- Sneller MC, Wang J, Dale JK, Strober W, Middleton LA, Choi Y, Fleisher TA, Lim MS, Jaffe ES, Puck JM, Lenardo MJ, Straus SE. Clinical, immunologic, and genetic features of an autoimmune lymphoproliferative syndrome associated with abnormal lymphocyte apoptosis. *Blood* 1997;89:1341-8.
- Canale VC, Smith CH. Chronic lymphadenopathy simulating malignant lymphoma. *J Pediatr* 1967;70:891-9.
- Sneller MC, Straus SE, Jaffe ES, Jaffe JS, Fleisher TA, Stetler-Stevenson M, Strober W. A novel lymphoproliferative/autoimmune syndrome resembling murine *lpr/gld* disease. *J Clin Invest* 1992;90:334-41.
- Watanabe-Fukunaga R, Brannan CI, Copeland NG, Jenkins NA, Nagata S. Lymphoproliferation disorder in mice explained by defects in Fas antigen that mediates apoptosis. *Nature* 1992;356:314-7.
- Rieux-Laucat F, Fischer A, Deist FL. Cell-death signaling and human disease. *Curr Opin Immunol* 2003;15:325-31.
- Sneller MC, Dale JK, Straus SE. Autoimmune lymphoproliferative syndrome. *Curr Opin Rheumatol* 2003;15:417-21.
- Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer* 1972;26:239-57.
- Leonardo M, Chan KM, Hornung F, McFarland H, Siegel R, Wang J, Zheng L. Mature T lymphocyte apoptosis-immune regulation in a dynamic and unpredictable antigenic environment. *Annu Rev Immunol* 1999;17:221-53.
- Dianzani U, Chiochetti A, Ramenghi U. Role of inherited defects decreasing Fas function in autoimmunity. *Life Sci* 2003;72:2803-24.
- Itoh N, Nagata S. A novel protein domain required for apoptosis. Mutational analysis of human Fas antigen. *J Biol Chem* 1993;268:10932-7.
- Nagata S. Apoptosis by death factor. *Cell* 1997;88:355-65.
- Suda T, Takahashi T, Golstein P, Nagata S. Molecular cloning and expression of the Fas ligand, a novel member of the tumor necrosis factor family. *Cell* 1993;75:1169-78.
- Wang J, Chun HJ, Wong W, Spencer DM, Lenardo MJ. Caspase-10 is an initiator caspase in death receptor signaling. *Proc Natl Acad Sci U S A* 2001;98:13884-8.

CONCLUSION

Autoimmune lymphoproliferative syndrome is a rare disease defined by the triad of chronic non-malignant enlargement of lymph nodes and spleen; increased number of α/β^+ DNTs; and impaired lymphocyte apoptosis in vitro. Individuals with ALPS frequently develop autoimmune cytopenias and have an elevated incidence of lymphomas. The etiology of ALPS has been attributed to dysregulation of lymphocyte homeostasis due to a primary defect in Fas-induced apoptosis. Future efforts directed at careful clinical follow-up and further scientific investigations are needed to learn more about the therapeutic interventions directed at altering the consequences of Fas mutations and to identify other genetic and/or environmental factors that may have a role in the pathogenesis of ALPS.

18. Kischkel FC, Lawrence DA, Tinel A, LeBlanc H, Virmani A, Schow P, Gazdar A, Blenis J, Arnott D, Ashkenazi A. Death receptor recruitment of endogenous caspase-10 and apoptosis initiation in the absence of caspase-8. *J Biol Chem* 2001;276:46639-46.
19. Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl-2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell* 1998;94:481-90.
20. De Maria R, Lenti L, Malisan F, d'Agostino F, Tomassini B, Zeuner A, Rippo MR, Testi R. Requirement for GD3 ganglioside in CD95- and ceramide-induced apoptosis. *Science* 1997;277:1652-55.
21. Bleesing JH, Straus SE, Fleisher TA. Autoimmune lymphoproliferative syndrome. A human disorder of abnormal lymphocyte survival. *Pediatr Clin North Am* 2000;47:1291-310.
22. Deutsch M, Tsopanou E, Dourakis SP. The autoimmune lymphoproliferative syndrome (Canale-Smith) in adulthood. *Clin Rheumatol* 2004;23:43-4.
23. Rieux-Laucat F, Blachere S, Danielan S, De Villartay JP, Oleastro M, Solary E, Bader-Meunier B, Arkwright P, Pondare C, Bernaudin F, Chapel H, Nielsen S, Berrah M, Fischer A, Le Deist F. Lymphoproliferative syndrome with autoimmunity: a possible genetic basis for dominant expression of the clinical manifestations. *Blood* 1999;94:2575-82.
24. Infante AJ, Britton HA, DeNapoli T, Middleton LA, Lenardo MJ, Jackson CE, Wang J, Fleisher T, Straus SE, Puck JM. The clinical spectrum in a large kindred with autoimmune lymphoproliferative syndrome caused by a Fas mutation that impairs lymphocyte apoptosis. *J Pediatr* 1998;133:629-33.
25. Oren H, Ozkal S, Gulen H, Duman M, Ucar C, Atabay B, Yilmaz S, Kargi A, Irken G. Autoimmune lymphoproliferative syndrome: report of two cases and review of the literature. *Ann Hematol* 2002;81:651-3.
26. Alvarado CS, Straus SE, Li S, Dale JK, Mann K, Le A, Lauer SJ. Autoimmune lymphoproliferative syndrome: a cause of chronic splenomegaly, lymphadenopathy, and cytopenias in children-report on diagnosis and management of five patients. *Pediatr Blood Cancer* 2004;43:164-9.
27. Avila NA, Dwyer AJ, Dale JK, Lopatin UA, Sneller MC, Jaffe ES, Puck JM, Straus SE. Autoimmune lymphoproliferative syndrome: a syndrome associated with inherited genetic defects that impair lymphocytic apoptosis-CT and US features. *Radiology* 1999;212:257-63.
28. Le Deist F, Emile JF, Rieux-Laucat F, Benkerrou M, Roberts I, Brousse N, Fischer A. Clinical, immunological, and pathological consequences of Fas-deficient conditions. *Lancet* 1996;348:719-723.
29. van der Burg M, de Groot R, Comans-Bitter WM, den Hollander JC, Hooijkaas H, Neijens HJ, Berger RM, Oranje AP, Langerak AW, van Dongen JJ. Autoimmune lymphoproliferative syndrome (ALPS) in a child from consanguineous parents: a dominant or recessive disease? *Pediatr Res* 2000;47:336-43.
30. Jackson CE, Fischer RE, Hsu AP, Anderson SM, Choi Y, Wang J, Dale JK, Fleisher TA, Middleton LA, Sneller MC, Lenardo MJ, Straus SE, Puck JM. Autoimmune lymphoproliferative syndrome with defective Fas: genotype influences penetrance. *Am J Hum Genet* 1999;64:1002-14.
31. Pensati L, Costanzo A, Ianni A, Accapezzato D, Iorio R, Natoli G, Nisini R, Almerighi C, Balsano C, Vajro P, Vegnente A, Levrero M. Fas/Apo1 mutations and autoimmune lymphoproliferative syndrome in a patient with type 2 autoimmune hepatitis. *Gastroenterology* 1997;113:1384-89.
32. Carter LB, Procter JL, Dale JK, Straus SE, Cantilena CC. Description of serologic features in autoimmune lymphoproliferative syndrome. *Transfusion* 2000;40:943-48.
33. Oliveira JB, Fleisher T. Autoimmune lymphoproliferative syndrome. *Curr Opin Allergy Clin Immunol* 2004;4:497-503.
34. Rieux-Laucat F, Deist FL, Fischer A. Autoimmune lymphoproliferative syndromes: genetic defects of apoptosis pathways. *Cell Death Differentiation* 2003;10:124-33.
35. Bleesing JJ, Brown MR, Novicio C, Guarraia D, Dale JK, Straus SE, Fleisher TA. A composite picture of TcR alpha/beta(+) CD4(-)CD8(-) T Cells (alpha/beta-DNTCs) in humans with autoimmune lymphoproliferative syndrome. *Clin Immunol* 2002;104:21-30.
36. Bleesing JJ, Brown MR, Straus SE, Dale JK, Siegel RM, Johnson M, Lenardo MJ, Puck JM, Fleisher TA. Immunophenotypic profiles in families with autoimmune lymphoproliferative syndrome. *Blood* 2001;98:2466-73.
37. Lopatin U, Yao X, Williams RK, Bleesing JJ, Dale JK, Wong D, Teruya-Feldstein J, Fritz S, Morrow MR, Fuss I, Sneller MC, Raffeld M, Fleisher TA, Puck JM, Strober W, Jaffe ES, Straus SE. Increases in circulating and lymphoid tissue interleukin-10 in autoimmune lymphoproliferative syndrome are associated with disease expression. *Blood* 2001;97:3161-70.

38. Tarazona R, DelaRosa O, Alonso C, Ostos B, Espejo J, Pena J, Solana R. Increased expression of NK cell markers on T lymphocytes in aging and chronic activation of the immune system reflects the accumulation of effector/senescent T cells. *Mech Ageing Dev* 2000;121:77-88.
39. Fuss IJ, Strober W, Dale JK, Fritz S, Pearlstein GR, Puck JM, Lenardo MJ, Straus SE. Characteristic T helper 2 T cell cytokine abnormalities in autoimmune lymphoproliferative syndrome, a syndrome marked by defective apoptosis and humoral autoimmunity. *J Immunol* 1997;158:1912-18.
40. Lim MS, Straus SE, Dale JK, Fleisher TA, Stetler-Stevenson M, Strober W, Sneller MC, Puck JM, Lenardo MJ, Elenitoba-Johnson KS, Lin AY, Raffeld M, Jaffe ES. Pathological findings in human autoimmune lymphoproliferative syndrome. *Am J Pathol* 1998;153:1541-50.
41. Maric I, Pittaluga S, Dale JK, Niemela JE, Delsol G, Diment J, Rosai J, Raffeld M, Puck JM, Straus SE, Jaffe ES. Histologic features of sinus histiocytosis with massive lymphadenopathy in patients with autoimmune lymphoproliferative syndrome. *Am J Surg Pathol* 2005;29:903-11.
42. Worth A, Thrasher AJ, Gaspar HB. Autoimmune lymphoproliferative syndrome: molecular basis of disease and clinical phenotype. *Br J Haematol* 2006;133:124-40.
43. Straus SE, Jaffe ES, Puck JM, Dale JK, Elkon KB, Rosen-Wolf A, Peters AM, Sneller MC, Hallahan CW, Wang J, Fischer RE, Jackson CM, Lin AY, Baumler C, Siegert E, Marx A, Vaishnav AK, Grodzicky T, Fleisher TA, Lenardo MJ. The development of lymphomas in families with autoimmune lymphoproliferative syndrome with germline Fas mutations and defective lymphocyte apoptosis. *Blood* 2001;98:194-200.
44. Gronbaek K, Straten PT, Ralfkiaer E, Ahrenkiel V, Andersen MK, Hansen E, Zeuthen J, Hou-Jensen K, Guldberg P. Somatic Fas mutations in non-Hodgkin's lymphoma: association with extranodal disease and autoimmunity. *Blood* 1998;92:3018-24.
45. Poppema S, Maggio E, van den Berg A. Development of lymphoma in Autoimmune Lymphoproliferative Syndrome (ALPS) and its relationship to Fas gene mutations. *Leuk Lymphoma* 2004;45:423-31.
46. Rao VK, Straus SE. Causes and consequences of the autoimmune lymphoproliferative syndrome. *Hematology* 2006;11:15-23.
47. Beltinger C, Kurz E, Bohler T, Schrappe M, Ludwig WD, Debatin KM. CD95 (APO-1/Fas) mutations in childhood T-lineage acute lymphoblastic leukemia. *Blood* 1998;91:3943-51.
48. Dianzani U, Bragardo M, DiFranco D, Alliaudi C, Scagni P, Buonfiglio D, Redoglia V, Bonisconi S, Corra A, Dianzani I, Ramenghi U. Deficiency of the Fas apoptosis pathway without Fas gene mutations in pediatric patients with autoimmunity/lymphoproliferation. *Blood* 1997;89:2871-79.
49. Drappa J, Vaishnav AK, Sullivan KE, Chu JL, Elkon KB. Fas gene mutations in the Canale-Smith syndrome, an inherited lymphoproliferative disorder associated with autoimmunity. *N Engl J Med* 1996;335:1643-49.
50. Bettinardi A, Brugnani D, Quiros-Roldan E, Malagoli A, La Grutta S, Corra A, Notarangelo LD. Missense mutations in the Fas gene resulting in autoimmune lymphoproliferative syndrome: a molecular and immunological analysis. *Blood* 1997;89:902-9.
51. Chiocchetti A, Indelicato M, Bensi T, Mesturini R, Giordano M, Sametti S, Castelli L, Bottarel F, Mazzarino MC, Garbarini L, Giacomelli F, Valesini G, Santoro C, Dianzani I, Ramenghi U, Dianzani U. High levels of osteopontin associated with polymorphisms in its gene are a risk factor for development of autoimmunity/lymphoproliferation. *Blood* 2004;103:1376-82.
52. Clementi R, Dagna L, Dianzani U, Dupre L, Dianzani I, Ponzoni M, Cometa A, Chiocchetti A, Sabbadini MG, Rugarli C, Ciceri F, Maccario R, Locatelli F, Danesino C, Ferrarini M, Bregni M. Inherited perforin and Fas mutations in a patient with autoimmune lymphoproliferative syndrome and lymphoma. *N Engl J Med* 2004;351:1419-24.
53. Clementi R, Chiocchetti A, Cappellano G, Cerutti E, Ferretti M, Orilieri E, Dianzani I, Ferrarini M, Bregni M, Danesino C, Bozzi V, Putti MC, Cerutti F, Cometa A, Locatelli F, Maccario R, Ramenghi U, Dianzani U. Variations of the perforin gene in patients with autoimmunity/lymphoproliferation and defective fas function. *Blood* 2006 May 23; Epub ahead of print.
54. Vaishnav AK, Orlicki JR, Chu JL, Krammer PH, Chao MV, Elkon KB. The molecular basis for apoptotic defects in patients with CD95 (Fas/Apo-1) mutations. *J Clin Invest* 1999;103:355-63.
55. Kasahara Y, Wada T, Niida Y, Yachie A, Seki H, Ishida Y, Sakai T, Koizumi F, Koizumi S, Miyawaki T, Taniguchi N. Novel Fas (CD95/APO-1) mutations in infants with a lymphoproliferative disorder. *Int Immunol* 1998;10:195-202.
56. Wu J, Wilson J, He J, Xiang L, Schur PH, Mountz JD. Fas ligand mutation in a patient with systemic lupus erythematosus and lymphoproliferative disease. *J Clin Invest* 1996;98:1107-13.

57. Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, Yao X, Puck JM, Straus SE, Lenardo MJ. Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. *Cell* 1999;98:47-58.
58. Zhu S, Hsu AP, Vacek MM, Zheng L, Schaffer AA, Dale JK, Davis J, Fischer RE, Straus SE, Boruchov D, Saulsbury FT, Lenardo MJ, Puck JM. Genetic alterations in caspase-10 may be causative or protective in autoimmune lymphoproliferative syndrome. *Hum Genet* 2006;119:284-94.
59. Chun HJ, Zheng L, Ahmad M, Wang J, Speirs CK, Siegel RM, Dale JK, Puck J, Davis J, Hall CG, Skoda-Smith S, Atkinson TP, Straus SE, Lenardo MJ. Pleiotropic defects in lymphocyte activation caused by caspase-8 mutations lead to human immunodeficiency. *Nature* 2002;419:395-9.
60. Dianzani U, Bragardo M, DiFranco D, Alliaudi C, Scagni P, Buonfiglio D, Redoglia V, Bonissoni S, Corra A, Dianzani I, Ramenghi U. Deficiency of the Fas apoptosis pathway without Fas gene mutations in pediatric patients with autoimmunity/ lymphoproliferation. *Blood* 1997;89:2871-9.
61. Siebel NL, Cossmann J, Magrath IT. Lymphoproliferative disorders. In: Pizzo PA, Poplack DG, eds. *Principles and Practice of Pediatric Oncology*, 3rd ed. Philadelphia: Lippincott-Raven Publishers, 1997: 589-609.
62. Teachey DT, Manno CS, Axsom KM, Andrews T, Choi JK, Greenbaum BH, McMann JM, Sullivan KE, Travis SF, Grupp SA. Unmasking Evans syndrome: T-cell phenotype and apoptotic response reveal autoimmune lymphoproliferative syndrome (ALPS). *Blood* 2005;105:2443-8.
63. van der Werff ten Bosch JE, Demanet C, Balduck N, Bakkus MH, De Raeve H, Desprechins B, Otten J, Thielemans K. The use of the anti-malaria drug Fansidar (pyrimethamine and sulphadoxine) in the treatment of a patient with autoimmune lymphoproliferative syndrome and Fas deficiency. *Br J Haematol* 1998;102:578-81.
64. van der Werff Ten Bosch J, Schotte P, Ferster A, Azzi N, Boehler T, Laurey G, Arola M, Demanet C, Beyaert R, Thielemans K, Otten J. Reversion of autoimmune lymphoproliferative syndrome with an antimalarial drug: preliminary results of a clinical cohort study and molecular observations. *Br J Haematol* 2002;117:176-188.
65. Ceretelli S, Petrini M, Galimberti S, Testi C, Frizzera G. Interferon-alpha activity in a case of severe autoimmune lymphoproliferative disease. *Ann Hematol* 2001;80:49-52.
66. Heelan BT, Tormey V, Amlot P, Payne E, Mehta A, Webster AD. Effect of anti-CD20 (rituximab) on resistant thrombocytopenia in autoimmune lymphoproliferative syndrome. *Br J Haematol* 2002;118:1078-81.
67. Rao VK, Dugan F, Dale JK, Davis J, Tretler J, Hurley JK, Fleisher T, Puck J, Straus SE. Use of mycophenolate mofetil for chronic, refractory immune cytopenias in children with autoimmune lymphoproliferative syndrome. *Br J Haematol* 2005;129:534-8.
68. Benkerrou M, Le Deist F, de Villartay JP, Caillat-Zucman S, Rieux-Laucat F, Jabado N, Cavazzana-Calvo M, Fischer A. Correction of Fas (CD95) deficiency by haploidentical bone marrow transplantation. *Eur J Immunol* 1997;27:2043-7.
69. Sleight BJ, Prasad VS, DeLaat C, Steele P, Ballard E, Arceci RJ, Sidman CL. Correction of autoimmune lymphoproliferative syndrome by bone marrow transplantation. *Bone Marrow Transplant* 1998;22:375-380.
70. Rao VK, Carrasquillo JA, Dale JK, Bacharach SL, Whatley M, Dugan F, Tretler J, Fleisher T, Puck JM, Wilson W, Jaffe ES, Avila N, Chen CC, Straus SE. Fluorodeoxyglucose positron emission tomography (FDG-PET) for monitoring lymphadenopathy in the autoimmune lymphoproliferative syndrome (ALPS). *Am J Hematol* 2006;8:81-85.